REMARKS

Claims 13, 20, 23, 24, 46 and 60 have been amended, and claims 13-27 and 46-60 are pending. In view of the above amendments and the following remarks, it is respectfully submitted that these claims are allowable.

Claims 13-16, 20-27, 46-52 and 56-60 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13-21 stand rejected under 35 U.S.C. §102(a) as being anticipated by Garbe, Blood Vol. 92, No. 10, Supplement 1, 165a, 1998. Claims 13-21 stand rejected under 35 U.S.C. §102(e) as being anticipated by Tedder, U.S. Patent No. 5,849,589. Claims 13-21 stand rejected under 35 U.S.C. §102(e) as being anticipated by Edelson, U.S. Patent No. 5,820,872. Claims 13-20 stand rejected under 35 U.S.C. §102(b) as being anticipated by Akagawa, et al., Blood 88:4029-4039, 1996. Claims 13-23 stand rejected under 35 U.S.C. §102(e) as being anticipated by Cohen et al., U.S. Patent No. 6,010,905.

Claims 24-27 stand rejected under 35 U.S.C. §`103(a) as being unpatentable over any one of Cohen, Garbe, Tedder, Edelson or Akagawa, in view of Patel, U.S. Patent No. 5,167,657. Claims 13-27 and 46-60 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Edelson, WO 97/34472, in view of any one of Tedder, Cohen or Garbe, and Patel.

Response to Claim Rejections Under 35 U.S.C. § 112

Claims 13, 24, 46 and 60 have been amended by substituting "or" for "and" in the listing of monocyte treatments. Applicant notes that any of the monocyte treatments listed in claims 13, 24, 46 and 60 may be used in the invention, and that monocytes may

be treated by more than one of the listed treatments. The claims are not intended to be limited to monocytes treated by only one of the listed treatments. Accordingly, this amendment is intended to clarify, and not to narrow, the claims.

Claims 13, 24, 46 and 60 have also been amended to clarify that the phrase "capable of forming photoadducts with cellular components" is intended to describe the type of photoactivatable agent used. This amendment is intended to clarify, and not to narrow, the claims.

Claims 20 and 27 have been amended by substituting "or" for "and". Applicant notes that the claim is intended to cover use of one or more of the recited growth factors, and the claims are not intended to be limited to use of only one of the recited growth factors. This amendment is intended to clarify, and not to narrow, the claims.

The Applicant respectfully traverses the Examiner's rejection of claims 15, 16, 47 and 48 under 35 U.S.C. §112, paragraph 2. The Examiner has rejected these claims as indefinite because the incubating period following treatment of the monocytes is recited using the terms "from about" and "to about." As described in the specification at page 10, lines 10-11, after the blood has been treated to induce differentiation of monocytes into dendritic cells, the treated monocytes must be incubated for a period of time sufficient to maximize the number of functional dendritic cells in the incubated cell population. As stated in the specification, the incubation period is typically from about 6 hours to about 48 hours. As discussed in the specification at page 18, line 18 through page 20, line 21, one skilled in the art can readily examine the composition using standard methods to determine when the incubation of the composition is sufficient to maximize the number of functional dendritic cells. Accordingly, claims 15, 16, 47 and

48 describe the subject matter covered with sufficient specificity to meet the requirements of 35 U.S.C. §112, paragraph 2. See W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

The Applicant also respectfully traverses the Examiner's rejection of claims 24 and 60 under 35 U.S.C. §112, paragraph 2 due to the use of the term "substantial amounts" in relation to leaching of plasticizer from the plastic bags. In the specification at page 10, lines 6-9, Applicant has described several plastic bags that can be used with the invention that do not leach a substantial amount of plasticizer as recited in amended claims 24 and 60. This description is sufficient to permit one of ordinary skill in the art to be reasonably apprised of the scope of the invention with sufficient specificity to meet the requirements of 35 U.S.C. §112, paragraph 2. See Andrew Corp. v. Gabriel Electronics, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988).

Claim 23 has been amended to correct a typographical error by changing "method" to "composition."

Response to Claim Rejections Under 35 U.S.C. § 102

The present claims, as amended, are directed to compositions comprised of functional dendritic antigen presenting cells derived from monocytes treated by exposure to physical perturbation, irradiation in the presence of a photoactivatable agent or treatment with a DNA binding agent. As described in the specification at page 5, lines 1-7, the composition includes a large number of functional dendritic cells generated in a period of only about 6 to 48 hours. Because the composition is comprised of dendritic cells that are formed in a relatively short period of time, the dendritic cells of the composition have a narrow age profile, that is the dendritic cells are relatively similar in

their age. This is an important characteristic of the composition, as dendritic cells will only phagocytize apoptotic cells during a specific period of their life cycle. Also, the dendritic cells will only present the antigens present in the apoptotic cells during a specific portion of their life cycle. Because the dendritic cells of the present invention are relatively close in age, the composition contains a maximum number of functional, antigen presenting dendritic cells.

As recited in amended claims 13 and 46 and in new claims 64 and 65, and described in the specification at, for example, page 9, lines 9-11 and 21-25, in one embodiment of the invention, induction of differentiation of monocytes into functional antigen presenting dendritic cells may be achieved by physical perturbation, such as by passing the monocytes through a narrow diameter plastic channel. The narrow diameter of the channel results in a relatively large surface area to volume ratio. As the monocytes in the fluid come into contact with the surface of the plastic channel, the monocytes repeatedly adhere to the plastic surface and are sheared from the surface by the force of the fluid flow through the channel. The forces experienced by the monocytes in this process induce a large number of the monocytes to differentiate into functional dendritic cells, more so than may occur with methods of physical perturbation such as centrifugation.

The age of the dendritic cells in the composition can be readily determined using methods known to those of ordinary skill in the art. For example, CD83 is a marker that can be used to determine the approximate age of dendritic cells. CD83 appears first in the cytoplasm of dendritic cells, and moves to the surface of the dendritic cells as the

dendritic cell ages. Accordingly, the presence and location of CD83 can be used to determine the relative age of the dendritic cells in a composition.

In another aspect, the present invention includes compositions comprised of functional antigen presenting dendritic cells that have been loaded with antigens from disease effector agents for presentation to T cells in the recipient. Apoptotic disease effector agents are presented to the functional dendritic cells, which phagocytize the apoptotic cells and present the antigens from the phagocytized cells at their surface. In a preferred embodiment, the disease effector cells are rendered apoptotic by photopheresis at the same time that the monocytes are exposed to photopheresis to induce differentiation into dendritic cells. The monocytes and apoptotic disease effector agents are co-cultivated to maximize the number of functional antigen presenting dendritic cells in the composition.

Garbe et al. describes the generation of dendritic cells from monocytes by standard cell culturing methods using a culture medium contained in a culture dish. As stated in the specification, these previously known cell culturing techniques take longer to induce the monocytes in the culture medium to form dendritic cells than the process of the present invention. As described in Garbe et al., the cell culturing process takes five days in contrast to only 6 to 48 hours in the process of the present invention. As a result, the age of the dendritic cells created by the cell culturing process used by Garbe will vary widely. Accordingly, a composition containing dendritic cells formed in the process described by Garbe et al. will not be as effective in presenting antigens because the dendritic cells will be formed at various times during culturing and will be at different points in their life cycle.

By contrast, because monocyte differentiation into dendritic cells occurs relatively rapidly in the process of the present invention, the resulting composition contains dendritic cells that are very close in age. As a result, the composition of the present invention contains a larger number of dendritic cells that are at the optimum stage in their life cycle to phagocytize apoptotic cells and subsequently present antigens from those phagocytized apoptotic cells. Garbe et al. does not teach or suggest a composition in which the dendritic cells are formed in a short time and in which the age of the dendritic cells in the composition is relatively uniform, much less recognize the advantages of such a composition. As described above, the age of the dendritic cells in the composition can be determined using methods known to those skilled in the art, such as, for example, by testing for the CD83 marker. Accordingly, Garbe et al. does not anticipate the composition of claims 13-21 of the present invention.

Similarly, Tedder et al., U.S. Patent No. 5,849,589 describes a method for inducing monocyte differentiation into dendritic cells using standard cell culturing methods and apparatus. While Tedder describes various improvements in these cell culturing methods, the compositions formed in the cell cultures described by Tedder all require several days to form. As a result, these compositions also contain dendritic cells that are at various stages of their life cycles. Tedder does not teach or suggest a composition containing dendritic cells in which the age of the dendritic cells is relatively uniform. Accordingly, Tedder does not anticipate the composition of claims 13-21 of the present invention.

Edelson, U.S. Patent No. 5,820,872, ("the Edelson '872 patent") describes methods for producing cellular vaccines containing a plurality of solid tumor derived

antigens admixed with antigen presenting cells. The antigen presenting cells described in the Edelson '872 patent are leukocyte preparations that have been subjected to photopheresis. As described in the Edelson '872 patent, the photopheresis treatment inactivates the leukocytes by inducing expression of empty MHC molecules on the surface of the leukocyte cells. See, e.g. Col. 6, lines 4-16. The method described in the Edelson '872 patent does not involve the induction of dendritic cells at all, but merely the induction of empty class I MHC molecules at the surface of antigen presenting cells already present in the subject's blood. Those empty class I MHC molecules are created by holding the antigen presenting cells at a lower-than-body temperature, thereby causing transport to the cell surface of empty, rather than filled, class I MHC molecules. See, e.g. Col. 6, lines 16-22. The tumor derived antigens can be externally loaded into the empty MHC molecules on the surface of the leukocytes for presentation of the antigen to T cells in the immune system. In marked contrast, the composition of the present invention is comprised of dendritic antigen presenting cells induced from monocytes. The Edelson '872 patent does not teach or suggest the use of functional dendritic cells in the treatment described, and the Edelson '872 patent does not teach or suggest a method for producing dendritic cells. Accordingly, the Edelson '872 patent does not anticipate the composition of claims 13-21 of the present invention.

Akagawa et al. describe the generation of dendritic cells from monocytes using standard cell culturing methods in various media. As described in Akagawa, the resulting compositions contained different types of dendritic cells, some of which did not have the ability to convert to macrophages. While Akagawa describes methods for inducing differentiation of monocytes under certain conditions, Akagawa does not teach or suggest

a composition containing an optimum number of functional antigen presenting dendritic cells such as the compositions recited in claims 13-20 of the present invention. Accordingly, Akagawa does not anticipate the composition of claims 13-20 of the present invention.

Cohen et al. describes methods for increasing the antigen presenting ability of blood monocytes by increasing the intracellular calcium level to increase the antigen presenting ability of the blood monocytes. As described in Cohen, this effect is a result of enhancing the effect of costimulatory molecule and MHC expression in the monocytes. The composition described in Cohen contains monocytes whose antigen presenting ability is enhanced. In contrast, the composition of the present invention is comprised of functional antigen presenting dendritic cells that have been induced from monocytes. Cohen does not teach or suggest a composition comprised of functional antigen presenting dendritic cells induced from monocytes. Accordingly, the Cohen reference does not anticipate the composition of claims 13-23 of the present invention.

Response to Claim Rejections Under 35 U.S.C. § 103

Patel, U.S. Patent No. 5,167,657, describes a plastic composition that can be used for the production of blood bags. As recognized by the applicant, blood bags of the type described in Patel were previously known in the art. The Patel reference does not discuss in any way the production of antigen presenting dendritic cells, the loading of dendritic cells with antigens, or the use of antigen presenting dendritic cells in immunotherapeutic treatment. Accordingly, the Patel reference does not add anything to the teachings of Garbe, Tedder, Edelson, Akagawa or Cohen regarding the compositions set forth in claims 24-27. For the reasons described above, these references do not teach or suggest

the compositions that are contained in the packaged preparations recited in claims 24-27. Accordingly, it is respectfully submitted that claims 24-27 are unobvious over Patel in view of Garbe, Tedder, Edelson, Akagawa or Cohen.

Edelson (WO97/34472) describes a method for extracorporeal treatment of blood to enhance the subject's immune system response, essentially a nonspecific adjuvant stimulatory effect. In the method described in the Edelson (WO97/34472) reference, extracorporeal blood is treated using photopheresis to enhance MHC expression on the cell surface. Dendritic cells may be introduced into the extracorporeal blood before or after the photopheresis step. See, e.g. page 14, lines 1-4. In the method described in the Edelson (WO97/34472) reference, the dendritic cells introduced into the blood are produced using previously known *in vitro* cell culture methods. See, e.g., page 19, line 19 to page 20, line 16. The dendritic cells may be antigen loaded by exposing the cultured dendritic cells to purified antigens prior to introduction of the dendritic cells into the blood. The Edelson (WO97/34472) reference states that the addition of dendritic cells to blood treated by photopheresis produces a synergistic effect that enhances the effectiveness of the photopheresis treatment. See, e.g., page 7, lines 7-17. Thus, the method described in the Edelson (WO97/34472) reference essentially enhances the effects of photopheresis described in the Edelson '872 patent by adding dendritic cells to the blood being treated by photopheresis. The dendritic cells added to the blood are produced outside of the photopheresis process.

The Edelson (WO97/34472) reference does not add anything to the teachings of Garbe, Tedder, Edelson, Akagawa or Cohen regarding the compositions set forth in claims 13-27 and 46-60. The Edelson (WO97/34472) reference does not teach or suggest

irradiating monocytes in the presence of a photoactivatable agent to produce functional antigen presenting dendritic cells. To the contrary, the dendritic cells used in the method described in the Edelson (WO97/34472) reference are prepared using previously known dendritic cell culture methods separately from the photopheresis treatment of the blood. Indeed, the Edelson (WO97/34472) reference states that the dendritic cells may be introduced either before or after the blood photopheresis step. Moreover, there is nothing in the Edelson (WO97/34472) reference that suggests that the method described in the Edelson '872 patent may be modified to produce functional antigen presenting dendritic cells by photopheresis. Accordingly, the Edelson (WO97/34472) reference in combination with Garbe, Tedder or Cohen and Patel would not teach or suggest to one of ordinary skill in the art the compositions set forth in claims 13-27 and 46-60 of the present application.

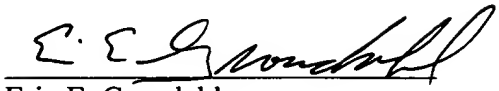
Conclusion

In view of the foregoing, it is respectfully submitted that claims 13-27 and 46-60 are allowable. Accordingly, favorable action on this application is requested at the earliest possible date. Should the Examiner have any questions regarding this Response or should the Examiner wish to discuss this case further, the Examiner is urged to contact the undersigned attorney at the telephone number listed.

On June 1, 2001, a Petition and Fee for Extension of Time Under 37 C.F.R. § 1.136(a)(1) was filed requesting an extension of time to respond to this Office Action from May 14, 2001 to August 14, 2001. Accordingly, no additional fees are believed to be required. However, if an additional fee is required, or to cover any deficiencies in fees paid, authorization is hereby given to charge our deposit account no. 50-1631.

Respectfully submitted,

Date: August 14, 2001

By 

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Marked Up Version of Amended Claims

13. (Amended) A composition comprising functional dendritic antigen presenting cells derived from monocytes which have been incubated following their treatment by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent, said photoactivatable agent being capable of forming photoadducts with cellular components, or (3) treatment with a DNA binding agent.

20. (Amended) The composition of claim 14, further comprising at least one of GM-CSF or IL-4.

23. (Amended) The composition of claim 22, wherein the disease effector agent is selected from the group consisting of disease-causing cells and microbes.

24. (Amended) A packaged preparation comprising:

a composition including functional dendritic antigen presenting cells derived from monocytes which have been incubated following their treatment by at least one of exposure to physical perturbation, irradiation in the presence of a photoactivatable agent, said photoactivatable agent being capable of forming photoadducts with cellular components, and treatment with a DNA binding agent; and

a container which does not leach substantial amounts of plasticizer and which is sufficiently porous to permit exchange of gases for storing the composition.

46. (Amended) A composition of co-incubated populations comprising:

a first population including disease effector agents which express at least one disease associated antigen; and

a second population including functional dendritic antigen presenting cells derived from monocytes which have been treated by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent, said photactivatable agent being capable of forming photoadducts with cellular components, or (3) treatment with a DNA binding agent.

60. (Amended) A packaged composition of co-incubated populations comprising:

a first population including disease effector agents which express at least one disease associated antigen;

a second population including functional dendritic antigen presenting cells derived from monocytes which have been treated by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent, said photoactivatable agent being capable of forming photoadducts with cellular components, or (3) treatment with a DNA binding agent; and

a container which does not leach substantial amounts of plasticizer and which is sufficiently porous to permit exchange of gases for storing the composition.